
Activation of neuronal gene expression by the JMJD3 demethylase is required for postnatal and adult brain neurogenesis.

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Public Summary:

The epigenetic mechanisms that enable lifelong neurogenesis from neural stem cells (NSCs) in the adult mammalian brain are poorly understood. Here, we show that JMJD3, a histone H3 lysine 27 (H3K27) demethylase, acts as a critical activator of neurogenesis from adult subventricular zone (SVZ) NSCs. JMJD3 is upregulated in neuroblasts, and *Jmjd3* deletion targeted to SVZ NSCs in both developing and adult mice impairs neuronal differentiation. JMJD3 regulates neurogenic gene expression via interaction at not only promoter regions but also neurogenic enhancer elements. JMJD3 localizes at neural enhancers genome-wide in embryonic brain, and in SVZ NSCs, JMJD3 regulates the *l12b* enhancer of *Dlx2*. In *Jmjd3*-deleted SVZ cells, *l12b* remains enriched with H3K27me3 and *Dlx2*-dependent neurogenesis fails. These findings support a model in which JMJD3 and the poised state of key transcriptional regulatory elements comprise an epigenetic mechanism that enables the activation of neurogenic gene expression in adult NSCs throughout life.

Scientific Abstract:

The epigenetic mechanisms that enable lifelong neurogenesis from neural stem cells (NSCs) in the adult mammalian brain are poorly understood. Here, we show that JMJD3, a histone H3 lysine 27 (H3K27) demethylase, acts as a critical activator of neurogenesis from adult subventricular zone (SVZ) NSCs. JMJD3 is upregulated in neuroblasts, and *Jmjd3* deletion targeted to SVZ NSCs in both developing and adult mice impairs neuronal differentiation. JMJD3 regulates neurogenic gene expression via interaction at not only promoter regions but also neurogenic enhancer elements. JMJD3 localizes at neural enhancers genome-wide in embryonic brain, and in SVZ NSCs, JMJD3 regulates the *l12b* enhancer of *Dlx2*. In *Jmjd3*-deleted SVZ cells, *l12b* remains enriched with H3K27me3 and *Dlx2*-dependent neurogenesis fails. These findings support a model in which JMJD3 and the poised state of key transcriptional regulatory elements comprise an epigenetic mechanism that enables the activation of neurogenic gene expression in adult NSCs throughout life.

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